European Journal of Internal Medicine 34 (2016) 2–10

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Narrative Review

Unique medical issues in adult patients with mucopolysaccharidoses

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ARTICLE INFO

Article history:
Received 25 March 2016
Received in revised form 13 May 2016
Accepted 15 May 2016
Available online 11 June 2016

Keywords:
Mucopolysaccharidoses
Adult
Disease management
Lysosomal storage diseases
Review
Enzyme replacement therapy

ABSTRACT

The mucopolysaccharidoses are a group of inherited metabolic diseases caused by deficiencies in enzymes involved in the sequential degradation of glycosaminoglycans (GAGs) leading to substrate accumulation in various tissues and organs. GAG accumulation can cause growth retardation and progressive damage to respiratory, cardiovascular, musculoskeletal, nervous, gastrointestinal, auditory, and visual systems. In the past, few people with severe phenotypic mucopolysaccharidosis (MPS) reached adulthood. However, better methods for diagnosis, multi-disciplinary care, and new therapies have extended lifespan, leading to an increasing number of patients surviving beyond childhood. The growing number of adult MPS patients poses significant challenges for clinicians who may not be familiar with the clinical manifestations of MPS. In addition, as new interventions have changed the natural history of these disorders, it is difficult to anticipate both the impact on life expectancy and other complications that may occur as these patients age. Because the MPS disorders are multi-organ diseases, their management requires a coordinated multi-disciplinary approach. Here we discuss the unique pattern of medical issues and multi-organ involvement in adult patients with MPS and identify the challenges that are associated with management of MPS. This review is based on information from an expert investigator meeting with MPS specialists held October 2–4, 2014 in Dublin, Ireland, as well as on current literature searches focusing on MPS and adults.

1. Introduction

The mucopolysaccharidoses are caused by deficiencies in enzymes involved in the sequential degradation of glycosaminoglycans (GAGs, hydrophilic polymers of highly modified hexose saccharides), which are ubiquitous in connective tissues. The resulting impaired degradation of GAGs in cells and tissues leads to substrate accumulation causing progressive multi-organ dysfunction [1]. Seven types of mucopolysaccharidosis (MPS) disorders have been described (Table 1), with MPS III and MPS IV each having two or more biochemical subtypes [1,2]. MPS I can be subdivided in three subtypes according to severity: Hurler syndrome (most severe), Hurler–Scheie syndrome, and Scheie

Abbreviations: DAS, Difficult Airway Society; ERT, Enzyme replacement therapy; GAGs, Glycosaminoglycans; HSCT, Hematopoietic stem cell transplantation; MPS, Mucopolysaccharidosis; QoL, Quality of life.

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http://dx.doi.org/10.1016/j.ejim.2016.05.017

Table 1
Overview of the mucopolysaccharidoses. Adapted from Muenzer et al, 2011 [1,2], with permission.

	Eponym	Deficient enzyme	Storage material
MPS I	Hurler, Hurler–Scheie, Scheie	α-L-iduronidase	Dermatan sulfate, heparan sulfate
MPS II	Hunter	Iduronate-2-sulfatase	Dermatan sulfate, heparan sulfate
MPS III	Sanfilippo	A: heparan N-sulfatase B: α-N-acetylglucosaminidase C: acetyl-CoA: α-glucosaminide acetyltransferase D: N-acetylglucosamine 6-sulfatase	Heparan sulfate
MPS IV	Morquio	A: N-acetylgalactose 6-sulfatase B: β-galactosidase	A: Keratan sulfate, chondroitin sulfate B: Keratan sulfate
MPS VI	Maroteaux–Lamy	Arylsulfatase B	Dermatan sulfate, chondroitin sulfate
MPS VII	Sly	β-Glucuronidase	Dermatan sulfate, heparan sulfate, chondroitin sulfate
MPS IX[a]	Hyaluronidase deficiency	Hyaluronidase	Hyaluronan

[a] Described in only four patients to date [2].

Fig. 1. Typical appearance of adults with severe forms of (left) MPS IVA showing short stature with short trunk and neck, profound skeletal and joint abnormalities and (middle) MPS VI showing short stature, broad or thickened facial features, and small hands showing some clawing. Right: patient with a non-classical phenotype of MPS IVA showing normal stature (reproduced from Hendriksz et al. [6], with permission).

syndrome (least severe). There are also neurological and non-neurological forms of MPS II.

All MPS disorders follow an autosomal recessive inheritance pattern, with the exception of MPS II, which is X-linked. Patients with MPS progressively develop growth impairment and deficiencies in respiratory, cardiovascular, musculoskeletal, nervous, gastrointestinal, auditory, and visual systems (Fig. 1, Table 2). Patients with MPS I, II, III, and VII may also exhibit learning difficulties and neurological decline [1]. Although MPS IV and VI are generally considered not to affect neurocognitive development, some patients may have an IQ below the normal range [3,4]. It remains to be elucidated if this is a direct result of the disease or indirectly results from reduced school attendance or

Table 2
Clinical manifestations and medical issues of the mucopolysaccharidoses and adult specialists who may be involved in the evaluation and/or management care of these manifestations [1,7–14].

Common clinical manifestations and medical issues	MPS types	Adult specialist
Musculoskeletal manifestations: deformities of the spine, thoracic cage, hips, knees, skull, and/or hands, short stature, joint abnormalities, joint pain, joint restriction/hypermobility	All types	Orthopedist, rheumatologist, physiotherapist
Spinal cord issues: spinal instability, cord compression, myelopathy	I, II, IV, VI	Neurologist, spine orthopedist, neurosurgeon, anesthesiologist
Ear, nose, throat manifestations, speech problems	All types	Otolaryngologist, speech therapist
Respiratory manifestations: upper and/or lower airway obstruction, restrictive disease, sleep-disordered breathing	All types	Otolaryngologist, pulmonologist, spine orthopedist
Cardiac manifestations: aortic and mitral valve insufficiency / stenosis, left ventricular hypertrophy, abnormal diastolic function, pulmonary hypertension	All types	Cardiologist, intensivist, anesthesiologist
Ocular manifestations: corneal clouding, refractive errors, glaucoma, papilledema	All types	Ophthalmologist
Cognitive decline, loss of motor function, behavioral problems, epilepsy	I (mainly Hurler, Hurler–Scheie), severe II, III, VII	Neurologist, psychiatrist, neuropsychologist
Abdominal manifestations: hepatomegaly, splenomegaly, umbilical/inguinal hernias, chronic diarrhea	All types	Gastroenterologist, general surgeon
Papular pearly rash across the scapulae, dermal melanocytosis, hirsutism	II, III, VI	Dermatologist
Carpal tunnel syndrome	I, II, VI	Neurologist, hand surgeon
Dental abnormalities: widely spaced and/or abnormally shaped teeth, weak enamel, gingival hyperplasia	I, II, IV, VI, VII	Dentist
Frequent surgery, diagnostic procedures requiring anesthesia	All types	Anesthesiologist
Follow-up of late effects/complications related to hematopoietic stem cell transplantation	Mainly MPS I-Hurler	Bone marrow transplant specialist
Reduced quality of life, depressed feelings	All types	Psychologist, psychiatrist
Coordination of care	All types	Clinical geneticist, metabolic physician, general physician